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## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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<b>(21) International Application Number:</b> PCT/EP91/00689 <b>(22) International Filing Date:</b> 9 April 1991 (09.04.91)  <b>(30) Priority data:</b> 20055 A/90 17 April 1990 (17.04.90) IT  <b>(71) Applicant (for all designated States except US):</b> EURAND INTERNATIONAL SPA [IT/IT]; Via M. de Vizzi, 60, I-20092 Cinisello B (IT).  <b>(72) Inventors; and</b> <b>(75) Inventors/Applicants (for US only) :</b> MAPELLI, Luigi, Giovanni [IT/IT]; Via Bettino Da Trezzo, 14, I-20125 Milan (IT). MARCONI, Marco, Giuseppe, Raffaele [IT/IT]; Via Aurora 6, I-20092 Cinisello Balsamo (IT). ZEMA, Marco [IT/IT]; Via Verga 10, I-22100 Como (IT).		<b>(74) Agents:</b> BROWN, Keith, John, Symons et al.; Wyeth Laboratories, Huntercombe Lane South, Taplow, Maidenhead, Berkshire SL6 0PH (GB).  <b>(81) Designated States:</b> AT (European patent), AU, BE (European patent), CA, CH (European patent), DE (European patent), DK (European patent), ES (European patent), FR (European patent), GB (European patent), GR (European patent), IT (European patent), JP, KR, LU (European patent), NL (European patent), SE (European patent), SU, US.  <b>Published</b> <i>With international search report.</i>
<b>(54) Title:</b> PHARMACEUTICAL FORMULATIONS  <b>(57) Abstract</b>  The taste of orally administered drugs is masked by coating the drug with a polymeric membrane which is soluble only at a pH of 5 or more. An acid substance is included in the formulation containing the coated drug to reduce or prevent the dissolution of the membrane in the oral cavity.		

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PHARMACEUTICAL FORMULATIONS

1 This invention relates to pharmaceutical  
formulations, particularly formulations in which the  
taste of orally administered drugs is masked, to the  
preparation of such formulations and to a method for  
5 masking the taste of orally administered drugs.

The oral administration of solid forms, for  
example tablets, often presents ingestion problems for  
the patient, especially in the case of children or old  
people. In order to get around this problem other  
10 forms of pharmaceutical formulations are resorted to,  
for example chewable tablets, tablets which disintegrate  
rapidly in the mouth or in a spoonful of water and  
monodose sachets, the contents of which are dissolved  
or suspended in a glass of water.

15 Unfortunately however many drugs have an  
unpleasant, bitter or irritating taste and therefore it  
is necessary to mask the taste. In order to mask the  
taste, particles of the drug may be coated with a  
membrane which prevents the release of the drug in  
20 water (if taken with water before ingestion) and in the  
oropharyngeal cavity during ingestion but liberates the  
drug after ingestion.

The most suitable membranes for this purpose are  
impermeable to water and saliva but dissolve as a  
25 function of the gastrointestinal pH. Among the most  
common membranes are those constituted by polymers  
which are insoluble in water or in acid environments  
but are soluble at pH greater than 5 as found in the  
intestine. However the pH of saliva is also greater  
30 than this value and so the partial dissolution of the  
membrane with consequent release of the unpleasant  
taste of the drug can begin in the oropharyngeal

cavity.

5 It has now been found that this difficulty can be avoided or minimized by adding acidic substances to the orally administered pharmaceutical forms such that the acidic substances dissolve to create a microenvironment around the coated particles, which prevents the dissolution of the polymers making up the membrane. Thus the taste masking is maintained in the oral cavity by the coating on the drug.

10 Accordingly the present invention provides a pharmaceutical formulation for oral administration comprising

15 a core comprising a drug, said core being coated with a polymeric membrane which is soluble only at a pH of 5 or greater

and an acidic compound for reducing or preventing the dissolution of the membrane in the oral cavity.

20 The core may, for example, be the drug itself eg in crystalline form or it may be a granulate containing the drug.

The formulation may be prepared by coating the core with a polymer which forms the polymeric membrane and adding the acidic compound to the formulation.

25 The invention also provides a method for masking the taste of drugs contained in pharmaceutical formulations, in which the taste of the drug is masked by coating with a polymeric membrane which is soluble only at a pH of 5 or greater characterised in that an acidic compound is added to the formulation in order to  
30 reduce or prevent the dissolution of the membrane in the environment of the oral cavity.

According to the invention the drug will be released only when the coated cores (ie particles) have passed through the stomach and reached the intestine where there is a pH equal to or greater than 5 (this occurs rapidly especially if the stomach is empty, and when dealing with particles of small dimensions).

Another proposal suggests that a taste masking action may be obtained with a membrane which is insoluble at a high pH (greater than 5) and soluble at a low pH (1.2 - 1.5) such as for example Eudragit E; this would be insoluble in the oral cavity (thus having a favourable effect on masking the taste) and soluble in the gastric tract. However if the passage of the product is particularly rapid, as can happen with particles of small dimensions and on an empty stomach, there is a risk of having an incomplete dissolution of the membrane and so an incomplete absorption of the drug.

The present invention also differs from that described in patent EP-A-0101418 where substances, e.g. carbohydrates and polysaccharides, are added to formulations containing drugs coated with, for example, semipermeable and pH independent membranes. These substances prevent or slow down the release of the drug across the membrane, whereas in the present invention, the acidic compounds prevent the dissolution of the membrane coating on the drug rather than the dissolution of the drug.

The invention is particularly suitable for drugs having a particularly unpleasant taste or which are irritating to the oral cavity; cited as illustrative, but not limiting examples, of these drugs are ibuprofen, sodium diclofenac, acetylsalicylic acid,

paracetamol, cimetidine, carboxymethylcysteine, Thiopronine, dextromethorphan hydrobromide, codeine and its salts, buflomedil, morphine and its salts, 5-aminosalicylic acid, macrolids and antibiotics such as penicillin and derivatives, erythromycin and its esters and ethers (eg roxithromycin), cephalosporins and tetracyclines.

Before coating it is convenient to granulate the drug although granulation is not essential.

The granulation is however useful for optimizing the granulometric distribution of the particles and may be carried out by using known dry (compacting) or wet techniques.

Preferably the core (eg comprising the drug in crystalline or granular form) has a size range of from 50, 100 or 200  $\mu\text{m}$  to 1500, 1200 or 700  $\mu\text{m}$ . Preferred size ranges are 100 to 1200  $\mu\text{m}$ , particularly 200 -700  $\mu\text{m}$ .

In order to mask the unpleasant taste of the drug, this is coated with a membrane comprising polymers having a pH dependent solubility and more particularly polymers insoluble in an acidic environment and soluble at pH 5 or higher.

As illustrative but not limiting examples of these polymers are cited: copolymers of methacrylic acid and methacrylic acid methyl ester (eg Eudragit L, Eudragit S), and copolymers of methacrylic acid ethyl ester (eg Eudragit L30D and L100-55), cellulose acetate phthalate, hydroxypropylmethylcellulose phthalate, polyvinyl acetate phthalate, shellac,

hydroxypropylmethylcellulose acetate succinate,  
carboxymethylcellulose, cellulose acetate trimellitate  
or a copolymer of maleic acid and phthalic acid  
derivatives.

5           The coating of the drug with these polymers may  
be carried out by known procedures such as the  
following:

          -individual stages or a combination thereof as  
exemplified in U.S.A. patents 3,415,758 and 3,341,416  
10           and in European Patent 0038585.

          -coating in coating pans as exemplified in  
Italian patent 929112 and in Canadian patent 879042

          -fluid bed coating as exemplified in U.S.A.  
patents 3,196,827 and 3,253,944 of D E Wurster.

15           The coated drug granules are very fine and  
irregular and therefore have a large surface area.  
Consequently the membrane is only a few micrometers  
thick, even when the percentage weight of the membrane  
is high, and thus in the brief time in which all or  
20           some of the particles remain, wholly or partially in  
the oral cavity, a dissolution or swelling, even  
partial, of the membrane can occur with consequent  
liberation of the unpleasant taste.

          It has now been found that this difficulty can be  
25           avoided or minimized according to the present invention  
if an acidic substance is added to the formulation in a  
quantity such as to maintain a microenvironment at a pH  
of less than 5 during the transit stage in the  
oropharyngeal cavity. Obviously the more acidic the  
30           microenvironment the better it is, although an excess  
of acid can itself give an unpleasant flavour.

5 It has been found that the optimum quantity of acid varies as a function of the weight of the final pharmaceutical formulation. Preferably 1% to 20% by weight of acid compound is used. As illustrative but not limiting examples of acid compounds the following are cited: fumaric acid, citric acid and tartaric acid.

10 Formulations of the invention may be in a pharmaceutical form which is easily taken by children, old people or patients with ingestion difficulty. Examples are tablet and monodose sachet formulations. Examples of tablets are those that can be chewed or dissolved in the mouth or disintegrate rapidly (eg within one minute) in a little (spoonful) of water; the monodose sachets can be taken directly or suspended in  
15 a small quantity of water (eg 20-50 ml).

The following Examples illustrate the invention.

#### EXAMPLE 1

##### (A) Preparation of the Granulate

20 Place 2000 g roxithromycin in a laboratory mixer, mix with an aqueous solution composed of 257 g of polyethyleneglycol 6000 and 600 g purified water.

Granulate with a 600  $\mu$ m mesh and dry the granulate at about 45°C. Utilise the fraction between 500 and 210  $\mu$ m.

##### 25 (B) Fluid Bed Coating of the Granulate

Place 360 g Eudragit L 100-55, 121 g 1N sodium hydroxide, 122.1 g talc, 36 g triethylcitrate, 57.8 g liquorice flavouring and 1910 g purified water in a



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stainless steel container equipped with stirrer.

Place 1500 g of granulate (A) in a Granu-Glatt fluid bed container equipped with a Wurster insert and spray 2250 g of the previously prepared suspension through the atomizer.

Dry the granules at about 50°C and sieve through the 600 µm mesh.

The release of the coated granules is determined in artificial juices according to the method described in USP XXII (Paddle, 200 rpm).

TIME (Minutes)	RELEASE DATE	
	pH 4.5	pH 6
- 15	12.3%	42.5%
- 60	-	80.6%

#### 15 (C) Preparation of the Tablets

Place 346.8 g microcrystalline cellulose, 66 g Kollidon CL, 18 g sodium saccharin, 90 g fumaric acid, 6 g sodium laurylsulphate, 12 g aerosil, 30 g strawberry flavour, 12 g magnesium stearate and 451.2 g granulate (B) in a cube mixer.

Mix for 20 - 25 minutes and compress.

A tablet of 172 mg contains 50 mg of roxithromycin.

The formulation of these tablets has been studied so that they disintegrate in less than 30 seconds in a spoonful of water or directly in the mouth. In order to conserve the masking of the taste, fumaric acid was added which maintains a microenvironment at a pH lower than that of the membrane solubility.

The protection obtained is satisfactory; in fact as one sees from the data reported in paragraph (B), the release at a relatively acid pH is low, thus the unpleasant taste of the drug is not noticeable.

5 The release is complete at a pH greater than 5 therefore the active ingredient will be liberated in the intestinal tract as soon as these pH values are reached, as the bioavailability tests have demonstrated.

#### EXAMPLE 2

##### (A) Preparation of the granulate

10 Place 1400 g ibuprofen in a laboratory mixer and mix with a solution composed of 210 g 95% ethyl alcohol and 37 g ethylcellulose.

Granulate with a 500  $\mu$ m sieve and dry the granulate at about 45°C. Use the fraction comprised between 500 and 210  $\mu$ m.

##### (B) Coating of the granulate by coacervation.

15 Form a solution of 1870 g purified water, 100 g cellulose acetate phthalate and 25.7 g sodium bicarbonate.

20 Prepare a solution containing 600 g sodium sulphate in 2800 g purified water. Put in a vessel the previously prepared cellulose acetate phthalate solution, 1500 g sodium sulphate solution and 600 g of granulate (A). Mix for about 5 minutes and add the remainder of the sodium sulphate solution.

25 Filter the microcapsule obtained and wash with water until the sodium sulphate is eliminated. Dry the microcapsules at about 50°C for 3 - 4 hours and sieve through the 600  $\mu$ m mesh.

30 The release of the coated granulate has been determined in artificial juices according to the method described in USP XXII (Paddle, 150 rpm).

TIME (Minutes)	RELEASE DATE	
	pH 1.2	pH 7.2
- 15	< 1%	-
- 30	-	90%

5 (C) Preparation of the Tablets

Into a cube mixer place 60 g microcrystalline cellulose, 70 g Kollidon CL, 4 g aspartame, 50 g fumaric acid, 1 g aerosil, 56 g strawberry flavour, 4 g liquorice flavour, 8 g magnesium stearate, 480 g granulate (B) and 80 g corn starch granulated with 2% of PVP K 30.

Mix for 20 - 25 minutes and compress.

One tablet of 406.5 mg contains 200 mg of ibuprofen.

15 Analogously to Example 1 the formulation of the tablets was studied in order to obtain a rapid disintegration in the mouth or in a spoonful of water and the fumaric acid was added to maintain the microenvironment at an acid pH.

20

EXAMPLE 3

(A) Preparation of the Granulate

Place 2000 g erythromycin in a laboratory mixer and mix for about 20 minutes with 1380 g of an aqueous solution of 15% hydroxypropylmethylcellulose.

25 Granulate through a 720  $\mu$ m mesh and dry in an oven at about 40°C for 15 - 20 hours.

Utilise the fraction included between 500 and 210  $\mu$ m.

(B) Coating of the Granulate in Fluid Bed

Place 550 g of the granulate (A) (500-210  $\mu$ m) in a UNI Glatt fluid bed container equipped with a Wurster insert and spray, through the atomizer, 7140 g of a solution having the following composition: 428.7 g hydroxypropylmethylcellulose phthalate, 21.3 g plasticizers, 1340 g ethyl alcohol, 5350 g methylene chloride.

Dry the granules at about 50°C. and sieve through a 600  $\mu$ m mesh.

The release of the coated granules was determined in artificial juices according to the method described in USP XXII (Paddle, 100 rpm)

TIME (Minutes)	RELEASE DATE	
	pH 1.2	pH 6
- 5	< 1%	-
- 15	< 1%	94%

(C) Preparation of the Monodose Sachets

In a cube mixer, place 2490 g sorbitol, 165 g of xanthan gum, 18 g PVP K30, 1.5 g sodium saccharin, 37.5 g citric acid, 112.5 g grapefruit flavour, 22.5 g talc, 0.4 g sodium docusate and 873 g Granulate (B).

Mix for 20 - 25 minutes and divide into sachets made of paper/aluminium/atoxic polyethylene and thermoseal.

One 2400 g monodose sachet contains 250 mg ethryomycin.

Analogously to the procedure in Examples 1 and 2, citric acid is added to the sachet formulation to maintain the acid pH and therefore the masking of the taste in the oropharyngeal cavity.

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Analogous results for the maintenance of the taste masking are obtained by the addition of acids in the final formulation when replacing erythromycin with cephalosporin or penicillin and their derivatives.

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CLAIMS

1. A pharmaceutical formulation for oral administration comprising  
a core comprising a drug, said core being coated with a polymeric membrane which is soluble only at a pH of 5 or greater  
and an acidic compound for reducing or preventing the dissolution of the membrane in the oral cavity.
2. A formulation as claimed in claim 1 wherein the acidic compound is fumaric acid, citric acid or tartaric acid or a mixture of one or more of said acids.
3. A formulation as claimed in claim 1 or 2 in which the acidic compound comprises 1 to 20% by weight of the pharmaceutical formulation.
4. A formulation as claimed in any one of claims 1 to 3 in which the polymeric membrane comprises a copolymer of methacrylic acid and methacrylic acid methyl ester or methacrylic acid ethyl ester, cellulose acetate phthalate, hydroxypropylmethylcellulose phthalate, polyvinyl acetate phthalate, shellac, hydroxypropylmethylcellulose acetate succinate, carboxymethylcellulose, cellulose acetate trimellitate or a copolymer of maleic acid and a derivative of phthalic acid.
5. A formulation as claimed in any one of claims 1 to 4 in which the drug is an antibiotic or ibuprofen.
6. A formulation as claimed in any one of claims 1 to 5 in which the size of the core is within the range 100 to 1200  $\mu\text{m}$ .

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7. A formulation as claimed in claim 6 in which the size of the core is within the range 200 to 700  $\mu\text{m}$ .

8. A formulation as claimed in any one of the preceding claims in the form of a tablet or sachet.

9. A process for preparing a pharmaceutical formulation as claimed in any one of claims 1 to 7 which comprises coating the core with a polymer to form the polymeric membrane and adding the acidic compound to the formulation.

10. A method for masking the taste of drugs contained in pharmaceutical formulations in which the taste of the drug is masked by coating with a polymeric membrane which is soluble only at a pH of 5 or more characterised in that an acidic compound is added to the formulation in order to reduce or prevent the dissolution of the membrane in the environment of the oral cavity.

# INTERNATIONAL SEARCH REPORT

International Application No PCT/EP 91/00689

<b>I. CLASSIFICATION OF SUBJECT MATTER</b> (if several classification symbols apply, indicate all) *		
According to International Patent Classification (IPC) or to both National Classification and IPC		
IPC <sup>5</sup> : A 61 K 9/50, A 61 K 9/52		
<b>II. FIELDS SEARCHED</b>		
Minimum Documentation Searched *		
Classification System	Classification Symbols	
IPC <sup>5</sup>	A 61 K	
Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched *		
<b>III. DOCUMENTS CONSIDERED TO BE RELEVANT *</b>		
Category *	Citation of Document, ** with indication, where appropriate, of the relevant passages <sup>12</sup>	Relevant to Claim No. <sup>13</sup>
X	EP, A, 0076515 (TANABE SEIYAKU) 13 April 1983 see claims 1-4; page 1, lines 23-25; page 2, lines 1-11; page 3, lines 1-6, 21-15; page 7, lines 5-18; page 8, line 10; example 1; page 10, lines 2-11 ---	1-10
X	EP, A, 0181564 (DR. G. GERGELY) 21 May 1986 see claims 1,6; page 2, paragraphs 3,4; page 4, paragraph 1; example 1 ---	1,2,3,5,9,10
X	EP, A, 0077264 (A.E.C. SOCIETE DE CHIMIE ORGANIQUE ET BIOLOGIQUE) 20 April 1983 see claims 1,10; page 4, lines 1-12; page 5, lines 17-18 -----	1,6-9
<div style="display: flex; justify-content: space-between;"> <div style="width: 48%;"> <p>* Special categories of cited documents: <sup>10</sup></p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> </div> <div style="width: 48%;"> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>"A" document member of the same patent family</p> </div> </div>		
<b>IV. CERTIFICATION</b>		
Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report	
26th June 1991	31 JUL 1991	
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**ANNEX TO THE INTERNATIONAL SEARCH REPORT  
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EP 9100689  
SA 46406

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 22/07/91  
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Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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